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Nerve Conduction Studies as an Objective Endpoint in Clinical Trials

FDA 2/2013

Definitions of minimal criteria for DSPN (Toronto 2011).

- 1. Possible Clinical DSPN:

  Symptoms *or* signs of DSPN.
- 2. Probable Clinical DSPN
- 3. Confirmed Clinical DSPN:

  An abnormal nerve conduction study and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy.
- 4. Subclinical DSPN:

  No signs *or* symptoms of polyneuropathy. An abnormal nerve conduction study

Diabetic Polyneuropathies: Update on Research Definition, Diagnostic Criteria and Estimation of Severity. Diabetes Metab Res Rev 2011;10.

A Trial of Proficiency of Nerve Conduction: Greater Standardization Needed (Dyck et al)

A Trial of Proficiency of Nerve Conduction: Greater Standardization Needed (Dyck et al)

- 4 groups of clinical neurophysiologists/technicians were given information on age, gender, height, and weight of the patients.
- All patients had DM but not all had DSPN.
- Patients' identity and polyneuropathy status witheld.
- Left leg warmed by immersion in hot water prior to the onset of testing; limbs maintained at 31-34^{o} C.
- 4 expert clinical neurophysiologists and their associate technologist
- No pre-training or consensus development preceding the trial.
- The evaluators independently performed NC tests using different EMG instruments, test peripherals, and their own procedures.
- Measured peroneal nerve amplitude (CMAP), conduction velocity (MNCV) and distal latency (MNDL), tibial CMAP, MNCV and MNDL, and sural sensory nerve amplitude (SNAP) and distal latency (SNDL) on the left leg of the same masked 24 patients on 2 consecutive days.
- Random assignment of patients and masking of patients.
- Clinical neurophysiologists indicated whether individual attributes were normal or abnormal and made a judgment of whether patients had electrodiagnostic evidence of DSPN.

Table 1 (Supplementary) - Raw Values of Clinical Neurophysiologists Measurements and Intra- and Inter-Observer Agreement of Measured Attributes of Nerve Conduction in Cl vs. NPhys Trial 3

Nerve Conduction Attribute	Cl NPhys	Day 1		Day 2		Friedman's χ^2 Test for Differences Among 4 Cl NPhys Teams				Wilcoxon Signed-Rank Test for Difference Between Day 1 & 2	
						Day 1		Day 2			
		Median	Range	Median	Range	χ^2	*p*	χ^2	*p*	S	*p*
Fibular CMAP (mV)	1	2.1	0.1 - 7.7	1.5	0.0 - 8.9	22.06	<0.01	33.10	<0.01	23.5	0.357
	2	2.2	0.0 - 7.3	2.7	0.0 - 8.4					52.0	0.069
	3	1.6	0.0 - 6.3	1.9	0.0 - 7.9					9.0	0.710
	4	2.4	0.0 - 7.8	2.5	0.0 - 9.5					2.5	0.930
Fibular MNCV (m/sec)	1	40.2	31.9 - 67.6	41.0	30.1 - 51.3	9.97	0.02	1.17	0.76	-45.0	0.148
	2	39.0	31.0 - 51.0	40.0	31.0 - 50.0					-0.5	1.000
	3	38.0	32.0 - 51.0	39.0	30.0 - 51.0					10.0	0.632
	4	40.0	31.0 - 50.0	39.0	31.0 - 49.0					27.0	0.319
Fibular MNDL (msec)	1	4.8	3.7 - 6.9	4.8	3.4 - 7.3	28.43	<0.01	36.55	<0.01	-11.5	0.699
	2	4.6	3.7 - 6.5	4.6	3.4 - 7.0					7.5	0.774
	3	4.4	3.4 - 6.9	4.5	3.3 - 7.4					-24.5	0.407
	4	5.0	3.8 - 7.1	5.1	3.7 - 7.8					44.5	0.099
Tibial CMAP (mV)	1	1.7	0.0 - 12.6	1.7	0.0 - 15.8	40.55	<0.01	32.03	<0.01	34.0	0.178
	2	3.9	0.0 - 17.8	3.8	0.0 - 17.6					-7.0	0.791
	3	2.1	0.0 - 14.9	2.5	0.0 - 13.1					-14.0	0.588
	4	3.6	0.0 - 19.2	3.4	0.1 - 18.0					17.0	0.616
Tibial MNCV (m/sec)	1	36.5	24.4 - 47.7	41.7	32.2 - 48.4	21.70	<0.01	12.95	<0.01	49.0	0.068
	2	40.0	35.0 - 54.0	43.0	35.0 - 52.0					5.5	0.826
	3	41.0	30.0 - 54.0	40.0	29.0 - 49.0					12.0	0.563
	4	42.0	33.0 - 49.0	41.0	15.0 - 52.0					40.0	0.167
Tibial MNDL (msec)	1	3.9	3.1 - 6.1	3.8	2.9 - 5.1	20.15	<0.01	39.14	<0.01	-46.0	0.111
	2	4.5	3.7 - 8.0	4.5	3.7 - 8.0					-15.5	0.576
	3	3.8	2.9 - 6.6	3.8	2.6 - 7.0					-8.5	0.725
	4	4.6	3.7 - 6.4	4.8	3.7 - 8.9					45.5	0.143
Sural SNAP (μV)	1	4.1	0.0 - 12.1	3.0	0.0 - 12.6	15.00	<0.01	15.20	<0.01	-2.5	0.917
	2	4.5	0.0 - 19.0	6.5	0.0 - 15.0					-11.0	0.519
	3	3.7	0.0 - 11.1	4.5	0.0 - 13.5					8.5	0.678
	4	3.0	0.0 - 14.0	3.0	0.0 - 12.0					3.5	0.699
Sural SNDL (msec)	1	3.9	3.1 - 4.6	3.8	3.0 - 4.5	15.16	<0.01	24.45	<0.01	-12.5	0.500
	2	4.0	3.2 - 5.0	4.1	3.1 - 4.4					3.0	0.868
	3	4.0	3.4 - 4.8	3.8	3.1 - 4.8					-11.5	0.386
	4	4.0	3.3 - 4.9	4.2	3.3 - 4.8					15.0	0.200

Conclusions:

- There was significant inter-observer variability that was attributed to differences in performance of NC.
- This was of sufficient magnitude to affect the conduct of therapeutic trials.
- To reduce the variability in therapeutic trials, the same electromyographers might perform all NCS assessments of individual patients.
- OR preferably NC procedures should be more standardized.

A Trial of Proficiency of Nerve Conduction: Greater Standardization Needed. (submitted) 2013

Inter- and Intra-examiner Reliability of Nerve Conduction Measurements in Normal Subjects (Chaudhry et al)

- Seven experienced electromyographers performed the studies and served as subjects using a random assignment.
- Each examiner was assigned 4 other individuals to examine on two occasions, separated by at least one week but at the same time of day.
- No one had access to the previous data at the time of the second study.
- A standardized nerve conduction protocol was followed.

Inter- and intra-examiner reliability of nerve conduction measurements in normal subjects. Ann Neurol 1991; 30(6):841-843.

Inter- and Intra-examiner Reliability of Nerve Conduction Measurements in Normal Subjects (Chaudhry et al)

- No significant differences were found between examiners in 8 of 12 attributes: sural CV, per. CMAP amp, per. F-wave lat, med. SNAP amp, med. sensory CV, med. motor DL, med. motor CV, and med. F-wave lat.
- Significant inter-examiner variability was noted for the remaining 4 attributes: sural SNAP amp., med. Motor CMAP amp., per. DL, and per. CV.
- No significant source of variance was found in the Intra-examiner analysis for any of the 12 attributes.

Conclusions from the studies:

- Longitudinal measurements should be performed by a single electromyographer whenever possible.
- In trials with multiple electromyographers, strict adherence to predetermined standardized techniques is critical.
- In general, sensory and motor conduction velocities and minimum F-wave latency show greater reproducibility on repeat testing.

How Well Do NCS Perform as a Surrogate Measure for Clinical Neuropathy Examination(Singleton et al)?

- Prospectiively studied 215 subjects with either diabetes or prediabetes and with or without neuropathy.
- Prediabetes defined by 2003 American Diabetes Association diagnostic criteria.
- Subjects had symptoms for less than 5 years, which excluded most subjects with severe neuropathy.
- Defined as having polyneuropathy if they had symptoms of neuropathy confirmed by abnormalities of at least two confirmatory electrodiagnostic, electrophysiological, or histological tests.
- Clinical evaluation using 3 validated scales: UENS, MDNS, NIS-LL
- The clinical scales were compared with NCS, QSART, QST, IENFD

The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy. J Peripher Nerv Syst 2008; 13(3):218-227.

Table 2. Baseline demographic and nerve function characteristics of subjects with and without neuropathy, using diagnostic criteria as described in the text.*

	No neuropathy, $N = 86$		Neuropathy, $N = 129$		
	Mean	SD	Mean	SD	Two-sided *t* test, p value
Subject characteristics					
Age	55.8	9.7	57.8	7.1	0.102
% female	50.0	–	54.2	–	0.578†
Body mass index	32.4	7.5	34.8	8.3	0.030
Neuropathy measures					
Exam scales					
UENS	1.39	2.29	9.24	6.10	<0.001
MDNS	0.83	1.76	6.62	5.13	<0.001
NIS-LL	0.91	1.82	7.23	5.51	<0.001
Electrophysiology					
SSA	11.6	6.6	5.0	5.4	<0.001
PMA	4.8	2.2	3.5	2.3	<0.001
PMCV	44.2	8.2	40.3	5.3	<0.001
CDT	53.1	27	78.8	23.8	<0.001
VDT	68.0	23.9	85.3	16.8	<0.001
QSART					
Ankle	1.11	0.77	0.76	0.73	0.001
Foot	0.94	0.72	0.67	0.73	0.008
IENFD					
Distal leg	4.6	2.7	1.7	2.3	<0.001
Distal thigh	6.8	3.51	4.52	2.99	<0.001
Pain					
Gracely	0.24	0.39	0.67	0.53	<0.001
VAS	6.3	13.8	24.2	27.3	<0.001

UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale; NIS-LL, Neuropathy Impairment Score–Lower Leg; SSA, sural sensory amplitude; PMA, peroneal motor response amplitude; PMCV, peroneal motor response proximal conduction velocity; CDT and VDT, cold and vibration detection thresholds; QSART, quantitative sudomotor axon reflex testing; IENFD, intraepidermal nerve fiber density; VAS, 100 mm visual analog scale.
*Comparison of means for each measure was performed with Student's *t* test, and two-sided p values are shown.
† Fraction of female subjects in each group was compared using 2 × 2 contingency table analysis and Fisher's exact test. Two-sided p value is shown.

Table 1. Correlation at baseline between examination scales, and with other measures of neuropathy severity in subjects with neuropathy.*

Exam scales	UENS	MDNS	NIS-LL
UENS	–	0.895 (<0.001)	0.863 (<0.001)
MDNS	–	–	0.880 (<0.001)
NIS-LL	–	–	–
Electrophysiology			
SSA	**−0.401 (0.002)**	−0.319 (0.002)	−0.249 (0.033)
PMA	−0.354 (0.001)	−0.311 (0.004)	−0.262 (0.017)
PMCV	**−0.278 (0.013)**	−0.183 (0.106)	−0.194 (0.087)
CDT	0.270 (0.014)	0.328 (0.002)	0.208 (0.059)
VDT	0.298 (0.006)	0.334 (0.003)	0.306 (0.005)
QSART			
Ankle	−0.179 (0.105)	−0.105 (0.343)	−0.068 (0.54)
Foot	**−0.331 (0.046)**	−0.087 (0.434)	−0.171 (0.123)
IENFD			
Distal leg	***−0.437 (0.001)***	−0.315 (0.008)	−0.186 (0.131)
Distal thigh	−0.239 (0.076)	−0.210 (0.087)	−0.204 (0.132)
Pain			
Gracely	**0.345 (0.001)**	0.279 (0.01)	0.214 (0.124)
VAS	**0.360 (0.002)**	0.211 (0.076)	0.199 (0.245)

UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale; NIS-LL, Neuropathy Impairment Score–Lower Leg; SSA, sural sensory amplitude; PMA, peroneal motor response amplitude; PMCV, peroneal motor response proximal conduction velocity; CDT and VDT, cold and vibration detection thresholds; QSART, quantitative sudomotor axon reflex testing; IENFD, intraepidermal nerve fiber density; VAS, 100 mm visual analog scale.

*Data are expressed as correlation coefficient (p value). Correlation coefficients were compared using a *t* test applied to the appropriately transformed difference between two dependent Pearson correlations *(Cohen and Cohen, 1983)*. Measures for which UENS was significantly ($p < 0.05$) better correlated than one other exam scale are shown in bold, and those for which UENS was significantly better correlated than both MDNS and NIS-LL are bolded and italicized. In contrast, NIS-LL or MDNS were not significantly better correlated than UENS with any baseline measure.

Conclusion:

- NCS show a mild to moderately strong correlation with clinical scales that have a relative large fiber focus (NIS-LL) vs small fiber focus (UENS).
- Overall, NCS have at least as strong an association with the clinical examination as other neuropathy measures e.g. QST, QSART and IENFD, with the exception of small fiber function where the IENFD shows a stronger association (specifically with the UENS).
- NCS are able to distinguish subject with neuropathy from those without neuropathy.
- NCS are not a sufficiently robust surrogate for clinical examination of neuropathy.

Relative Sensitivity of NCS Measures in Detecting Recent Onset of Neuropathy in Prediabetes

- 50 subjects with IGT or IFG (prediabetes).
- Prospective study using standardized methodology for all electrodiagnostic studies.
- Evidence of symptomatic clinical peripheral neuropathy and an abnormality in at least one of the following: NCS, QST, or QSART. Abnormal IENFD was NOT required.

Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. Muscle Nerve. 2009; 39(4):529-535.

Conclusion:

- The relative sensitivity of electrodiagnostic studies in detecting recent onset of neuropathy was QSART>QST>NCS.
- However electrophysiological studies were not as sensitive as the distal leg intraepidermal nerve fiber density (IENFD).
- For most subjects, no single electrophysiological test was abnormal. There was overlap in abnormal tests.
- in a multicenter study of neuropathy, combinations of tests would be required as endpoint measures.

Despite Concerns with NCS as Outcome Measures for Neuropathy, How do they perform in Actual Clinical Studies: DCCT/EDIC:?

- The Diabetes Control and Complications Trial (DCCT) enrolled 1,441 patients with type 1 diabetes and randomly assigned them to intensive or conventional treatment.
- The DCCT demonstrated that reducing glucose levels delayed or prevented the development of diabetic complications including neuropathy over a mean of 6.5 years.
- At DCCT closeout, subjects were encouraged to maintain or begin intensive treatment.
- Were invited to participate in a prospective observational study (Epidemiology of Diabetes Interventions and Complications [EDIC]) to evaluate the long-term effects of prior treatment on microvascular outcomes, including neuropathy.

Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care 2010; 33(5):1090-1096.

Important Note on NCS Measurements in DCCT/EDIC:

- NCS in the DCCT and EDIC were very rigorously performed.
- A training manual was used.
- Performance of the study was standardized.
- Temperature measurements were very carefully controlled.

Table 2—*Prevalence of clinical (symptoms and signs) and NCS results suggestive of distal symmetrical polyneuropathy at DCCT baseline, DCCT closeout, and EDIC years 13–14*

Variable	DCCT baseline	DCCT closeout	EDIC years 13–14
Clinical examination			
Symptoms			
INT	32 (5)	44 (7)*	119 (20)†
CONV	39 (7)	75 (13)	172 (30)
Abnormal sensation			
INT	128 (21)	147 (25)†	248 (41)*
CONV	120 (21)	206 (36)	292 (50)
Abnormal reflexes			
INT	105 (18)	135 (23)†	264 (44)
CONV	93 (16)	212 (37)	292 (50)
Clinical neuropathy			
INT	57 (10)	88 (15)†	204 (34)†
CONV	48 (8)	128 (22)	240 (41)
Electrophysiology			
Abnormal NCS			
INT	185 (31)	164 (28)†	326 (54)†
CONV	196 (34)	288 (50)	401 (69)
Primary outcome			
Confirmed clinical neuropathy			
INT	39 (7)	52 (9)†	152 (25)†
CONV	31 (5)	97 (17)	204 (35)

Data are *n* (%). *$P < 0.01$ former intensive treatment group (INT) vs. former conventional treatment group (CONV). †$P < 0.001$ INT vs. CONV.

Conclusions:

- In a randomized trial with carefully performed NCS, abnormalities of NCS are effective outcome measures in neuropathy.
- For diabetic neuropathy, highly significant differences could be detected 6.5 and 13 years after initiation of the study.
- While this is true for an intervention where there is a robust effect, it may not be true for interventions where the effect is small.

Clinically Meaningful Changes in NCS

- The minimum clinically detectable change was determined to be 2 points in the mean NIS and corresponds to a:
- 1 mV change in the mean ∑CMAP (sum of the ulnar, peroneal and tibial CMAP amplitudes)($p < 0.01$).
- 1 μV in the mean ∑SNAP (sum of ulnar and sural SNAP amplitudes)($p < 0.001$).
- 1 μV in the mean sural SNAP ($p < 0.01$).

Sural nerve myelinated fiber density differences associated with meaningful changes in clinical and electrophysiological measurements. J Neurol Sci 1996; 135:114-117.

- To detect a change of 2 points in the NIS in a 2-year study, one would require 68 patients in each treatment arm to have a power of 0.90, using a two-sided test at the 0.05 level.

Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester diabetic neuropathy study cohort. Neurology 1997; 49:229-239.

Overall Conclusions for NCS as an Outcome Measure in Neuropathy:

- Rigorous control over all aspects of NCS performance is critical: temperature, distance measurements, electrode placement, electrode type, stimulation sites, measurements, recording etc.
- Standardization must be insured across all sites in the study.
- Certain NCS measures e.g. conduction velocities may show a higher degree of reproducibility.